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EXAMINER	
MOORE, WILLIAM W	
ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/884,456	HOUGHTON ET AL.	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 27-43 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 27-43 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Amendment

Applicant's Preliminary Amendment filed, July 27, 2001, cancels the original claims 1-26 and presents the new claims 27-43. Claims 27-31 are drawn to compositions that comprise polynucleotides encoding hepatitis C virus polypeptides comprising, in claim 27, a generic hepatitis C virus NS3 protein designated a protease at pages 6-8 of the specification, and, in claims 28-31, compositions comprising polynucleotides encoding "active" proteases that include amino acid sequences of, variously, the undecapeptide of SEQ ID NO: 63, the nonapeptide of SEQ ID NO:64, the 202-amino acid protein of SEQ ID NO:65 which includes both of SEQ IDs NOs:63 and 64, or, in claim 28, the amino acid sequence of SEQ ID NO:1 which is identical to the amino acid sequence of SEQ ID NO:65 required by claim 31. Claims 32 and 34-36 are drawn to expression vectors comprising polynucleotides encoding hepatitis C virus polypeptides that are fusion polypeptides joining one of the regions set forth in claims 27 or 29-31 with an undesignated "fusion partner", and claim 33 indicates that human superoxide dismutase is a specific fusion partner. Claims 37-41 are drawn to expression vectors comprising polynucleotides encoding hepatitis C virus polypeptides comprising, in claim 37, a generic hepatitis C virus NS3 protein designated a protease at pages 6-8 of the specification, and, in claims 38-41, compositions comprising polynucleotides encoding "active" proteases that include amino acid sequences of, variously, the undecapeptide of SEQ ID NO: 63, the nonapeptide of SEQ ID NO:64, the undecapeptide of SEQ ID NO: 63, the nonapeptide of SEQ ID NO:64, the 202-amino acid protein of SEQ ID NO:65 which includes both of SEQ IDs NOs:63 and 64, or, in claim 38, the amino acid sequence of SEQ ID NO:1 which is identical to the amino acid sequence of SEQ ID NO:65 required by claim 41. Finally claims 42 and 43 are drawn to expression vectors

comprising polynucleotides encoding hepatitis C virus polypeptides that are fusion polypeptides joining the regions set forth in claim 37 with, in claim 42, an undesignated "fusion partner" while claim 43 indicates that human superoxide dismutase is a specific fusion partner. No pending claim excludes the presence in a polynucleotide, whether a polynucleotide of claims 27-31 or a polynucleotide a encoding fusion protein of claims 32-36, of a nucleic acid sequence region encoding more of the initial hepatitis C virus translation product, termed a polyprotein at page 5 of the specification, in addition to a region encoding the NS3 region, which the specification states comprises a protease in its amino-proximal portion. Even compositions of claim 33 and expression vectors of claim 43, which follow a definitional statement at page 10 of the specification indicating that a "fusion partner" is a non-HCV protein, permit a polynucleotide encoding hepatitis C virus polypeptides of claims 32 and 42 from which they depend to include more than the amino-terminal region of the NS3 protein.

Claim Rejections - 35 USC § 101

35 U.S.C. § 101 reads as follows:
Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 27-31 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter.

Claims 27-31 cannot describe patentable subject matter where they claim a product of Nature, rather than a composition made by a person, because a composition can not properly comprise an "isolated" polynucleotide and a "composition" that comprises a polynucleotide encoding an hepatitis C virus "proteolytic polypeptide" comprising some or all or a "NS3 domain protease" is also the hepatitis C virus itself.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude"

granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 27-43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 5,371,017. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compositions comprising polynucleotides of claims 27-36 herein, and the expression vectors of claims 38-43 herein, both comprise nucleotide sequences that encode proteases and fusion proteins having hepatitis C virus protease amino acid sequences required by the proteases and the fusion proteins encoded by nucleotide sequences in the polynucleotides of compositions of the patented claims 1-7 and nucleotide sequences in the expression vectors of the patented claims 8-14.

Claim 36 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 15 of copending Application No. 10/438,313, which is an application for reissue of U.S. Patent No. 5,371,017. Although the conflicting claims are not identical, they are not patentably distinct from each other because the composition of claim 36 herein comprises a polynucleotide having a nucleotide sequence that encodes a fusion protein having the amino acid sequence region necessary for proteolytic activity present in the fusion protein amino acid sequence required by limitations of the co-pending claim 15. This is a provisional obviousness-type double patenting rejection because the conflicting claim has not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27, 32, 33, 37, 42, and 43 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification fails to exemplify or describe the preparation of compositions that comprise polynucleotides of claim 27, and the preparation of an expression vector of claim 32, where the claims recite no structural feature of a generic "proteolytic hepatitis C virus polypeptide". This is because the specification fails to identify a polynucleotide encoding an amino acid sequence constituting a proteolytic hepatitis C virus polypeptide comprising a generic NS3 domain protease, providing a structure meeting the definition at page 6 of the specification: "an enzyme derived from HCV which exhibits proteolytic activity . . . encoded in the NS3 domain of the HCV genome". Nothing in the specification indicates that at the time application serial No. 07/680,296 - the first to provide the disclosure of the instant application - was filed on April 4, 1991, Applicant possessed a polynucleotide comprising a region encoding a polypeptide specified by any particular region of the HCV genome, or possessed a polynucleotide encoding a fusion polypeptide comprising a polypeptide specified by any particular region of the HCV genome, that could recognize and cleave a particular substrate, whether a peptide or polypeptide comprising an amino sequence set forth at page 21, lines 13-15, of the specification or some other substrate. The results that Example 5 suggests at pages 31 and 32 of the specification cannot be shown to have been caused by a proteolytic activity of a hepatitis C virus-encoded protein, or domain, present in Applicant's particular fusion protein expressed in *E. coli* host cells where it failed to include a peptide sequence actually recognized and cleaved by as much of the NS3 domain "protease" the fusion polypeptide comprised, thus products detected by ELISA in that Example can only be produced by the activity of endogenous host cell proteases.

The specification does not otherwise show that Applicant had prepared either a polynucleotide compositions of claims 27, or a vector of claim 32, capable of encoding a proteolytic HCV polypeptide that could cleave any particular viral or peptide substrate where the disclosure of Example 6 is hypothetical in its description of recovery of an active protease and disclosures of Examples 8-10 are hypothetical in their descriptions of expression of an active protease either in yeast cells or in an *in vitro* transcription and translation system. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. §112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification nowhere furnishes relevant identifying characteristics of a proteolytic hepatitis C virus protease, or fusion protein, in a claimed composition that can cleave or proteolytically process an hepatitis C virus polyprotein, or any portion thereof, or any other particular polypeptide or peptide. Indeed, the subsequent disclosures of Tomei et al., 1994, Lin et al., 1994, De Francesco et al., 1996, Ramanathan et al. 1996, Lin et al., 1997, and Thomson et al., 1997, made record herewith, indicate the contrary: that another region, termed the NS4A cofactor, in the hepatitis C virus polyprotein, a region not encoded by a nucleic acid sequence in any of Applicant's expression vectors of Examples 5-11, must be present together with the NS3 protein's amino-proximal region in order to produce proteolytic activity specific to an hepatitis C virus protease.

Claims 27-43 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the preparation of compositions and expression vectors that comprise polynucleotides encoding a polypeptide that comprises a catalytic component of a hepatitis C virus protease comprising the amino acid sequence set forth in SEQ ID NO:66, does not reasonably provide enablement for preparation of compositions and expression vectors that comprise polynucleotides encoding a proteolytically active hepatitis C virus protease, whether or not fused to a fusion partner. The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the invention commensurate in scope with these claims.

Although the specification identifies, e.g., in the amino acid sequence of SEQ ID NO:66, a region in the hepatitis C virus NS3 protein with sequence characteristics of a serine protease and makes the appropriate analogies between the hepatitis C virus NS3 product and proteolytic products located in analogous regions of polyproteins encoded by the RNA genomes of other flaviviruses, it provides no guidance for the preparation of claimed compositions comprising polynucleotides, or expression vectors comprising polynucleotides, that encode polypeptides, or fusion proteins, capable of the proteolytic processing of a hepatitis C virus polyprotein. This is because the specification does not describe, thus cannot enable, an integral hepatitis C virus protease capable of cleaving a defined substrate. In addition, the small peptide regions encoded by polynucleotides and expression vectors of claims 29, 30, 34, 35, 39, and 40 are insufficient to support proteolysis even if Applicant's disclosure had provided guidance for finding regions of the polyprotein encoded by the hepatitis C virus genome that could provide specificity.

It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying factors stated in *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986)). Applying the enablement analysis set forth in *Wands* to Applicant's disclosure, it is apparent that:

a) the specification lacks adequate, specific, guidance for determining those portions of the hepatitis C virus polyprotein amino acid sequences that provide specific recognition of the native cleavage sites in the polyprotein,

b) the specification lacks working examples wherein any polynucleotide or expression vector described by claims 27-43 is shown to properly recognize and cleave any portion of the hepatitis C virus polyprotein, or a peptide substrate based on the predicted cleavage sites, and,

c) in view of the publications made of record herein, the state of the art and level of skill in the art at the time the instant disclosure was first filed do not support the identification of other, distant, regions of flavivirus or hepatitis C virus translation products that confer proper cleavage specificity.

Thus the scope of the claimed subject matter cannot be considered to be supported by the disclosure of the present specification.

The following is a quotation of the second paragraph of 35 U.S.C. §112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-37, 42 and 43 rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 27, 32, 33, 42 and 43 are indefinite because claims 27, 32, and 37, from which claims 33, 42 and 43 depend, recite, "compris[ing] an HCV NS3 domain protease or an active . . . truncation analog", and one of ordinary skill in the art cannot tell what is meant by the term "domain" where the specification provides no specific, structural, description which domain is intended. The public and the artisan attempting to establish the scope of the claimed subject matter cannot determine what is more than a "domain", thus excluded by the claim, or what is less than a "domain", included in a truncation analog of the claim. Claims 33, 42 and 43 are included in this rejection because they depend from claim 32 but fail to resolve the ambiguity of the term "domain".

Claims 27-36 are indefinite because claims 27 and 32, from which claims 28-31 and 33-36 depend, recite "[a] composition comprising an isolated . . . polynucleotide" where no polynucleotide can remain an "isolated" polynucleotide if present in a composition. Thus the public and the artisan cannot determine the meets and bounds of the intended subject matters.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 27-31 are rejected under 35 U.S.C. § 102(b) as being anticipated by Reyes et al., WO 90/00597, made of record herewith.

Published over a year before the instant application was filed, the Example 2 at page 29 of Reyes et al. anticipates claims 27-31 in disclosing the preparation of hepatitis C virus particles. This is because a composition cannot properly comprise an "isolated" polynucleotide and because a composition that comprises a polynucleotide encoding an hepatitis C virus "proteolytic polypeptide" that comprises some or all or a "NS3 domain protease" is also the hepatitis C virus particle itself.

Claims 27-31 are rejected under 35 U.S.C. § 102(b) as being anticipated by Choo et al., EP 318216, made of record herewith.

Published over a year before the instant application was filed, the Example IV.A.1. at pages 27-28 29 of Choo et al. anticipates claims 27-31 in disclosing the preparation of hepatitis C virus particles in a supernatant prepared from infected chimpanzee plasma, as well as the subsequent extraction of the hepatitis C virus genome from the viral particles into an aqueous composition. This is because no composition can properly comprise an "isolated" polynucleotide and a composition comprising a polynucleotide which encodes an hepatitis C virus "proteolytic polypeptide" comprising some or all or a "NS3 domain protease" is also the hepatitis C virus itself.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a

whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 27-43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Miyamura et al., U.S. 5,372,928, in view of Miller et al., 1990, Proceedings of the National Academy of Sciences, U.S.A., Vol. 87, pages 2057-2061, Bazan et al., 1989, Virology, Vol. 171, pages 637-639, and Gorbalenya et al., 1989, Nucleic Acids Research, Vol. 17, pages 3889-3897, all made of record herewith.

For purposes of this rejection, the recitation in claims 27 and 32 of, "comprising an isolated polynucleotide which encodes an hepatitis C virus proteolytic polypeptide . . . compris[ing] an HCV NS3 domain protease or an active HCV NS3 domain protease truncation analog", and the similar recitation in claim 37 of, "comprises a polynucleotide encoding said HCV proteolytic polypeptide compris[ing] an HCV NS3 domain protease or an active HCV NS3 domain protease truncation analog", are construed to describe polynucleotides encoding polypeptides that need not be the initially translated hepatitis C virus polyprotein but comprise at least a portion of its NS3 domain.

Miyamura et al. is available under 35 U.S.C. § 102(e) as prior art to claims 27-43 herein in view of the September 15, 1989, filing date of their priority application serial No. 07/408,045, which discloses the portions of their patent this rejection relies on. Miyamura et al. teach a polynucleotide encoding the polyprotein of the hepatitis C virus 1 strain in Figures 12A-C and also teach the relative positions of the structural and the non-structural domains within the hepatitis C virus 1 polyprotein wherein the "putative NS3 [domain extends] from about amino acid 1007 to about amino acid 1650". See, cols. 6-7 and Figure 11, and particularly col. 7 at lines 8-10. Miyamura et al. need not teach an amino acid sequence in Figures 12A-C because determining the amino acid

sequence of the encoded polyprotein would have been routine in the art at the time the invention was made and the polyprotein amino acid sequence was indeed disclosed in the priority application serial No. 07/408,045. Miyamura et al. also teach that functions of domains within the hepatitis C virus polyprotein may be predicted on the basis of similarities shared by the amino acid sequences of flaviviruses and the hepatitis C virus amino acid sequence and that a protease function resides in the amino acid sequences of flavivirus NS3 domains. See col. 17 at lines 5-21. These teachings have priority to September 15, 1989, when they appeared in the parent application serial No. 07/408,045. While Miyamura et al. do not teach how to identify an amino acid sequence region with a protease function and are silent about the presence or absence of other viral functions residing in the NS3 domain of a flavivirus or hepatitis C virus polyprotein, they teach preparation of cloning vectors, and transformed host cells comprising the vectors, comprising inserts of specific, defined, regions found anywhere in a nucleic acid sequence encoding all or part of an hepatitis C virus polyprotein in Examples I-IV at cols. 28-39.

Miyamura et al. explicitly teach, at cols. 8-10, that expression vectors comprising transcriptional and translational regulatory elements operably linked to a polynucleotide encoding a desired regions of the hepatitis C virus polyprotein should be used to produce desired portions of the hepatitis C virus polyprotein in host cells, and further suggest preparation of expression constructs providing fusions of hepatitis C virus amino acid sequence regions with proteins commonly used in the art as fusion partners such as β-galactosidase and superoxide dismutase [SOD]. See, col. 14, line 41, through col. 15, line 14.

Miller et al. teach, Figure 2, the identification of the amino acid sequence of the helicase region within the NS3 domain of an hepatitis C virus polyprotein, relying upon

the disclosure of Houghton et al. ('216) and comparisons with flavivirus helicase amino acid sequences. Miller et al. specifically teach, at page 2060, right column, that three conserved peptide regions allow them to align a 190-amino acid sequence disclosed in EP 0318216, but not identified therein as a helicase domain, with NS3 domain helicase regions of a flavivirus and a plant potyvirus. Bazan et al., 1989, teach that the amino-terminal third of the NS3 domains of flavivirus polyproteins comprise a serine protease region having sequence homology with cellular serine proteases, and that a helicase amino acid sequence region is characteristically present in NS3 domains of flavivirus polyproteins carboxyl-proximal to the protease region. Bazan et al., 1989, specifically teach, see, e.g., Figure 1 and its legend, that proposed flavivirus and pestivirus protease regions have particularly conserved amino acid sequences in the immediate vicinity of the residues of the catalytic triad – histidine, aspartate and serine – of a serine protease and that distances between these three catalytic amino acids are uniformly conserved in the primary structures of the protease regions among the flaviviruses. Bazan et al. additionally teach, at page 637, that flavivirus proteases probably cleave amino acid sequences after pairs of basic amino acids.

Gorbalenya et al. similarly teach that flaviviruses and pestiviruses have protease regions in the amino-terminal portions of NS3 domains, that amino acid sequences in the immediate vicinity of residues of the catalytic triad are particularly conserved, and that the distances between the three catalytic amino acids are uniformly conserved in primary structures of protease regions among flaviviruses. See Figure 1 and its legend. Gorbalenya et al. further teach, at page 3889, that these proteases "are probably involved in the processing of the viral non-structural proteins."

In view of the teachings of Miyamura et al. that the functions of the domains within the hepatitis C virus polyprotein may be predicted on the basis of similarities shared by

the amino acid sequences of flaviviruses and hepatitis C virus and that a protease function resides in the amino acid sequence of flavivirus NS3 domains, as well as their structural teachings of the entire coding sequence for an hepatitis C virus polyprotein and the amino positions of the encoded amino acid sequence that are the boundaries of the NS3 domain in hepatitis C virus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to translate the polyprotein encoded by the DNA sequence of Figure 12 of Miyamura et al., compare the consensus flavivirus protease amino acid sequences of Bazan et al. and Gorbalenya et al. with the amino-proximal region of the hepatitis C virus NS3 domain having the boundaries taught by Miyamura et al., and prepare a polynucleotide encoding only an hepatitis C virus protease in order to insert it in an expression vector, or within a vector providing a fusion construct, to then produce the protease or fusion protein. The instant specification discloses no purification of claimed protease polypeptides or fusion polypeptides, thus combination of teachings of Miyamura et al., Bazan et al., and Gorbalenya et al. renders obvious subject matter commensurate with the scope of the instant specification.

This is because both Bazan et al. and Gorbalenya et al. agree on structural features that can identify key amino acid sequence regions of NS3 domain proteases of flaviviruses and because Miyamura et al. teach that amino acid sequences of flaviviruses are predictive of structures and features of hepatitis C virus amino acid sequences and also teach how to prepare polynucleotide coding sequences from anywhere within the hepatitis C virus genome in order to insert them in expression vectors and fusion constructs to recombinantly produce the encoded region. Such an artisan would have been motivated to do so because Gorbalenya et al. teach that NS3 domain proteases are probably involved in processing of the viral non-structural proteins, thus integral to the infection process. Such an artisan would have had a

reasonable expectation of success in applying the teachings of Gorbalenya et al. and Bazan et al. to identify a polynucleotide of Figure 12 of Miyamura et al. that encodes a protease comprising the amino-terminal region of the NS3 domain because Miller et al. successfully used amino acid sequence comparison of flavivirus and hepatitis C virus to identify the helicase region in the carboxyl terminus of the hepatitis C virus NS3 domain.

Miyamura et al. is available as prior art under 35 U.S.C. § 102(e) because it is the work of another and because its parent application 07/408,045 provides a priority date of September 15, 1989, in its Figures 6-1 through 6-9, including the deduced amino acid sequence, for the disclosure of Figures 12A-C. Miller et al., Bazan et al., and Gorbalenya et al. are available as prior art under 35 U.S.C. § 102(a) because they were published within a year of the relevant date of April 4, 1990. Thus, some or all of these disclosures might be displaced as prior art by a Declaration of the co-inventors under 37 CFR 1.131.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is now 571.272.0933. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can now be reached at 571.272.0928. The fax phone numbers for all communications for the organization where this application or proceeding is assigned remains 703.872.9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is now 571.272.1600.

William W. Moore
June 25, 2004

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600